Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers.

Bibliographic Source(s)

Huang ET, Mansouri J, Murad MH, Joseph WS, Strauss MB, Tettelbach W, Worth ER, UHMS CPG Oversight Committee. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med. 2015 May-Jun;42(3):205-47. [86 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The grades of recommendations (strong or conditional) and levels of evidence (high, moderate, and low) are defined at the end of the "Major Recommendations" field.

Recommendations

1. In patients with Wagner Grade 2 or lower diabetic foot ulcers (DFUs), the committee suggests against using hyperbaric oxygen (HBO_2) therapy (very low-level evidence in support of HBO_2, conditional recommendation).
2. In patients with Wagner Grade 3 or higher DFUs that have not shown significant improvement after 30 days of treatment, the committee suggests adding HBO_2 to the standard of care to reduce the risk of major amputation and incomplete healing (moderate-level evidence, conditional recommendation).
3. In patients with Wagner Grade 3 or higher DFUs who have just had a surgical debridement of an infected foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; incision and drainage [I&D] of deep space abscess; or necrotizing soft tissue infection), the committee suggests adding acute post-operative HBO_2 to the standard of care to reduce the risk of major amputation and incomplete healing (moderate-level evidence, conditional recommendation).

Definitions

Levels of Evidence

High: Further research is very unlikely to change confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate of effect.

Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate of effect.

Very low: Any estimate of effect is very uncertain.

Strength of Recommendations and Implications for the General Population, Healthcare Workers and Policy-Makers

Strong

- *Population* - Most people in this situation would want the recommended course of action, and only a small proportion would not.
- *Healthcare Workers* - Most people should receive the recommended course of action.
- *Policy-Makers* - The recommendation can be adapted as a policy in most situations.

Conditional

- *Population* - The majority of people in this situation would want the recommended course of action, but many would not.
- *Healthcare Workers* - Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision-making.
- *Policy-Makers* - There is a need for substantial debate and involvement of stakeholders.

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Wagner Grade 3 DFU Algorithm
- Algorithm for the Use of HBO_2

Scope

Disease/Condition(s)

Diabetic foot ulcers (DFUs)

Guideline Category

Management

Risk Assessment

Treatment

Clinical Specialty

Dermatology

Family Practice

Infectious Diseases

Internal Medicine

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Plans

Managed Care Organizations

Patients

Physician Assistants

Physicians

Podiatrists

Guideline Objective(s)

To rate the quality of evidence and generate practice recommendations for the treatment of diabetic foot ulcers (DFUs)

Target Population

Diabetic patients who have or are at risk for foot ulcers

Interventions and Practices Considered

Hyperbaric oxygen (HBO_2) therapy

Major Outcomes Considered

- Critical outcomes
  - Major amputation
  - Incomplete healing at one year
- Important outcomes
  - Resolution of infection
  - Quality of life
  - Minor amputation

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search Strategy

The committee identified published systematic reviews of hyperbaric oxygen (HBO_2) therapy for diabetic foot ulcers (DFUs) and cross-referenced them to identify randomized controlled trials (RCTs) and observational studies (OBSs) of interest (see Table 4 in the original guideline document).

OBSs included any non-randomized comparative studies using either historical or contemporary control groups. The committee decided to include OBSs because the number of available RCTs was small and was unlikely to answer all the questions about the various types of patients included in the scope of this guideline. The committee then performed a subsequent librarian-assisted search of the Medline, EMBASE and Cochrane databases to identify if there were any RCTs that were not included in the published systematic reviews. Search dates included articles published up through April 2015. Medical Subject Headings (MeSH) terms were used. The keywords "leg ulcers," "diabetes" and "hyperbaric oxygenation" were used, along with their synonyms. A detailed search strategy is included in Appendix A of the original guideline document.

Trial Selection

Titles and abstracts from the search results were independently reviewed by two panelists to select potentially relevant articles. The inclusion criteria were RCTs comparing patients with DFUs with a control group. The committee eliminated studies if they did not include the populations as defined by the Patient, Intervention, Comparison and Outcomes (PICO) questions, if they did not include the outcomes of interest, or if they did not include a comparison group.

Evidence Review

The review committee identified nine RCTs and 21 OBSs for initial review. The subsequent formal review included 655 references but did not identify any additional RCTs that were not previously identified from the systematic reviews. Studies were eliminated from consideration if they did not report data on the outcomes of interest or did not include patients in the specific study populations (see Table 9 in the original guideline document).

Two of the OBSs may have had overlapping datasets, so only the larger data set was evaluated.

Number of Source Documents

Five of the randomized controlled trials (RCTs) were included for this analysis (see Table 10 in the original guideline document). The remaining studies were excluded because they did not report data on the preselected outcomes.

Five of the observational studies (OBSs) were included for this analysis (see Table 12 in the original guideline document). The remaining studies were excluded because they either did not report data on the preselected outcomes or failed to provide a comparison group.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Further research is very unlikely to change confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate of effect.

Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate of effect.

Very low: Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis of Observational Trials

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

Two panelists independently extracted the data using predetermined criteria and presented the summary of evidence to the remainder of the panel to reach consensus. The committee attempted to contact authors of studies to obtain original trial data if the committee could not identify clear patient groups, but they did not receive any replies to their inquiries.

Statistical Techniques

Meta-analysis of relevant randomized controlled trials (RCTs) and observational studies (OBSs) was carried out using the Revman software package (Review Manager, version 5.2). A description of statistical terms is provided in Table 5 of the original guideline document. The committee pooled outcome data using the number of events and sample size of the control and experimental groups reported in published manuscripts. The results were depicted in a forest plot showing the individual effect sizes as well as the weighted pooled summary effect size with confidence intervals. The committee calculated the I^2 as a measure of heterogeneity. The I^2 statistic represents the proportion of variability that is attributable to heterogeneity rather than chance or random error. The higher the I^2 statistic is, the greater the degree of heterogeneity. When heterogeneity was judged to be substantial, the committee rated down the quality of evidence. There is no specific I^2 cutoff point above which the evidence is rated down for heterogeneity. An arbitrary cutoff of 50% is often used, but this is paired with a judgment of whether the majority of studies support a specific action and whether the observed heterogeneity is clinically meaningful (i.e., a very high I^2 may not be important if the difference in effect size is not clinically important across studies).

The committee presented results using risk ratios (i.e., relative risk) for binary outcomes and mean differences for continuous outcomes. Peto odds ratio was used when events were rare (small or zero events). Considering the heterogeneity of available studies, the committee decided *a priori* to use the random effects model for meta-analysis. The random effects model takes into account the variation in effect size between studies. In cases where there was only one study to analyze, the committee calculated a simple odds ratio and confidence interval.

Rate Quality of Evidence for Each Outcome

The committee constructed summary of evidence tables and assessed the risk of bias of the studies. Whenever possible, the committee used intention-to-treat analysis (even if the original manuscripts did not report it in this manner) by using a worst-case scenario assuming healing in the control group and failure to heal in the study group. This data matrix allowed reviewers to extract evidence profiles for each of the five outcomes from the entire body of literature. RCTs and OBSs were both analyzed, and the body of literature (RCT vs. OBS) with the highest level of evidence was used for decision-making. If there was equivalent level of evidence and the magnitude of effect was similar, the RCTs and OBSs were analyzed together. If there was equivalent level of evidence but the magnitude of effect was dissimilar, only the RCT studies were used.

The committee applied the relevant factors outlined in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence up (more reliable) or down (less reliable) (see Table 6 in the original guideline document), and assigned a final rating for each outcome for each Patient, Intervention, Comparison and Outcomes (PICO) question. In many analyses, the effect size was large or very large (i.e., two to five times reduction in relative effect). The committee opted to rate up only one level (as opposed to two for very large effect). It is also reasonable to not rate up in the presence of factors that lead to rating down. This decision is explicit in the tables that describe the committee's judgments and process. This semi-quantitative "score" corresponds to an overall quality of evidence rating using the four-tiered GRADE quality levels (very low; low; moderate; and high) (see Table 7 in the original guideline document).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Oversight Committee

The Oversight Committee consisted of a representative from the Undersea and Hyperbaric Medical Society (UHMS) Board of Directors, the UHMS Oxygen Therapy Committee, the UHMS Quality, Utilization, Authorization and Reimbursement Committee, the UHMS Publications Committee, the UHMS International Membership, and a member of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. The Oversight Committee is tasked with the development of a series of clinical practice guidelines (CPGs) for the

appropriate use of hyperbaric oxygen (HBO_2). The Oversight Committee invites potential members of the CPG review committee based on individual areas of expertise, which may or may not include HBO_2. The Oversight Committee reviews curriculum vitae of potential members and evaluates each candidate for potential conflicts of interest using responses to a questionnaire detailing the potential reviewers' financial interests involving the HBO_2 indication in question.

Review Committee

CPG review committee members were oriented to the review process and GRADE methodology using slide presentations, reading lists and webcasts. Review committee members were then asked to participate in the multi-step process.

Formulation of Questions and Selection of Outcomes

The first task of the Review Committee is to create a list of clinically relevant questions to be answered in the guideline. These questions are created using the Patient, Intervention, Comparison and Outcomes (PICO) format. This approach allows for the creation of a clearly defined patient population, an intervention to be compared with an alternative treatment, and a set of clinical outcomes rated on a nine-point scale defining that outcome as critical, important, or not important.

The term "standard wound care" is meant to represent the optimal management of surgical debridement, mechanical offloading, infection control, revascularization and metabolic control. Pre-HBO_2 treatment of Wagner Grade 3 and 4 diabetic foot ulcers (DFUs) is assumed to include surgical excision of all devitalized tissues. These four questions were formulated by the Review Committee:

1. For a patient with a DFU, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?
2. For a patient with a Wagner Grade 2 or lower DFU that has not shown significant improvement after 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?
3. For a patient with a Wagner Grade 3 or higher DFU that has not shown significant improvement after 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?
4. For a patient with a Wagner Grade 3 or higher DFU who has just had a surgical debridement of the foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; incision and drainage [I&D] of deep space abscess; or necrotizing soft tissue infection), is acute postoperative HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?

Formulating Recommendations

A final rating of the quality of evidence (across all outcomes) was given based on the critical outcome with the lowest level of evidence. The Review Committee then formulated recommendations for each PICO question. This step required assigning a level of strength for each recommendation using the two-tiered GRADE levels (conditional or strong) (see Table 8 in the original guideline document). The final recommendations were agreed upon by consensus.

Patient Engagement

Two groups of patients with DFU were invited to participate in the formulation of this guideline. Both patients who had received HBO_2 therapy and patients who had not received HBO_2 were included. The first group was recruited from a wound and hyperbaric medicine clinic to answer an online survey rating the outcomes selected by the Review Committee using a nine-point scale. This activity was approved by an Institutional Review Board (IRB). The second group was recruited from a wound and hyperbaric medicine clinic to attend a face-to-face meeting with members of the Review Committee using video conferencing technology. The CPG development process and recommendations were presented to the patients. The Review Committee solicited patient perspective on multiple issues ranging from their fears and concerns at their initial consultation to their view of the successes and failures of their treatment course. The values, opinions and perspectives of these patients are reported in the original guideline document.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations and Implications for the General Population, Healthcare Workers and Policy-Makers

Strong

- *Population* - Most people in this situation would want the recommended course of action, and only a small proportion would not.

- *Healthcare Workers* - Most people should receive the recommended course of action.
- *Policy-makers* - The recommendation can be adapted as a policy in most situations.

Conditional

- *Population* - The majority of people in this situation would want the recommended course of action, but many would not.
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- *Policy-makers* - There is a need for substantial debate and involvement of stakeholders.

Cost Analysis

Cost-effectiveness

Few studies have been published regarding the cost-effectiveness of hyperbaric oxygen (HBO_2) therapy in the treatment of diabetic foot ulcers (DFUs). One author reported in a cohort study of 41 patients that the estimated cost (in 1991 dollars) of below-knee amputation (US$40,000) plus rehabilitation (US$30,000) was greater than the cost of HBO_2 to salvage a limb (US$31,265). Another author reported 2003-2004 Australian data that the average cost for wound care and HBO_2 was AUS$14,928 for each amputation prevented, and that HBO_2 might decrease the overall cost of healthcare when the costs of amputation and rehabilitation were considered. One study used 2008 Canadian data on DFU prevalence and HBO_2 efficacy data to create a computer model that estimated the 12-year cost for patients receiving HBO_2 was CND$40,695, compared with CND$49,786 for standard care alone. This study concluded that adjunctive HBO_2 for DFU was cost-effective when compared to standard care. Only a single randomized controlled trial (RCT) prospectively addressed the cost-effectiveness of the use of HBO_2 in the treatment of DFUs. This study evaluated the cost of ulcer dressings per visit per patient for one year in both the treatment and control groups and found an average savings of UK£2,960 per patient treated with HBO_2. This analysis took into account the additional costs of HBO_2 and treatment of any associated complications. The Review Committee was unable to obtain the raw data for this study to include it in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis.

Due to recent trends in insurance coverage and reimbursement policies, the cost-effectiveness of HBO_2 is likely to become an important factor in any discussions focusing on the use of HBO_2 in clinical practice. Cost-effectiveness studies are often conducted using decision modeling and simulations (e.g., Markov, Monte Carlo) due to the complex economic variables and uncertainty involved. Thus, it is somewhat challenging to interpret the significance of cost-effectiveness data using these existing studies.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

External Review

The Undersea and Hyperbaric Medical Society (UHMS) Oversight Committee reviewed the document before undergoing additional review by content experts. Content experts included specialists who treat diabetic foot ulcers (DFUs) but who do not provide hyperbaric oxygen (HBO_2) treatment. Once the review committee addressed any concerns, the document was posted for public comment. After the review committee addressed any public comments, the manuscript was submitted for publication. All public comments and committee responses are posted on the UHMS Web site (www.uhms.org/cpg).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of hyperbaric oxygen (HBO_2) therapy in the treatment of diabetic foot ulcers (DFUs)

Potential Harms

There are obviously some adverse events that are solely related to hyperbaric oxygen (HBO_2) and would not be seen in patients treated with alternative therapies (i.e., barotrauma, central nervous system oxygen toxicity, hyperoxic myopia). Data from one management company revealed 463,293 monoplace hyperbaric chamber treatments of 17,267 patients from 2009-2010. In 2009, there were 916 adverse events reported for 207,479 treatments in 7,781 patients (adverse event rate of 0.44%), and in 2010 there were 954 adverse events reported for 255,814 treatments in 9.296 patients (adverse event rate of 0.37%). In order of decreasing rate of occurrence were ear pain (20 per 10,000 treatments), confinement anxiety (eight per 10,000), hypoglycemic events (five per 10,000), shortness of breath (two per 10,000), seizures (two per 10,000), sinus pain (one per 10,000), and chest pain (one per 10,000). Overall, the risk of adverse events from HBO_2 can be considered to be very low and self-limited when they do occur.

Qualifying Statements

Qualifying Statements

Clinical Practice Guidelines are developed to be of assistance to hyperbaric physicians and other healthcare professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of healthcare providers and each patient's individual circumstances.

The Undersea and Hyperbaric Medical Society (UHMS) makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Huang ET, Mansouri J, Murad MH, Joseph WS, Strauss MB, Tettelbach W, Worth ER, UHMS CPG Oversight Committee. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med. 2015 May-Jun;42(3):205-47. [86 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 May-Jun

Guideline Developer(s)

Undersea and Hyperbaric Medical Society - Medical Specialty Society

Source(s) of Funding

Undersea and Hyperbaric Medical Society

Guideline Committee

Undersea and Hyperbaric Medical Society (UHMS) Diabetic Foot Ulcer (DFU) Clinical Practice Guideline (CPG) Review Committee

Composition of Group That Authored the Guideline

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Oversight Committee Members: Enoch T. Huang, John Feldmeier, Ken LeDez, Phi-Nga Jeannie Le, Jaleh Mansouri, Richard Moon, M. Hassan Murad

Financial Disclosures/Conflicts of Interest

Enoch T. Huang, MD, MPH & TM - Less than 25% of Dr. Huang's clinical practice income involves hyperbaric oxygen (HBO_2) as an adjunctive therapy for managing diabetic foot ulcers (DFU).

Warren S. Joseph, DPM - Dr. Joseph has no financial relationship with the clinical practice of hyperbaric medicine.

Jaleh Mansouri, MD, MPH - Dr. Mansouri is contracted to be the methodologist (paid consultant) for the Undersea and Hyperbaric Medical Society (UHMS) clinical practice guideline (CPG) Project. Dr. Mansouri has no financial relationship with the clinical practice of hyperbaric medicine.

M. Hassan Murad, MD, MPH & TM - Less than 5% of Dr. Murad's clinical practice income involves HBO_2 as an adjunctive therapy for managing DFU.

Michael B. Strauss, MD - Less than 10% of Dr. Strauss's clinical practice income involves HBO_2 as an adjunctive therapy for managing DFU.

William H. Tettelbach, MD - Less than 25% of Dr. Tettelbach's clinical practice income involves HBO_2 as an adjunctive therapy for managing DFU.

Eugene R. Worth, MD - Less than 25% of Dr. Worth's clinical practice income involves HBO_2 as an adjunctive therapy for managing DFU.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Undersea and Hyperbaric Medical Society (UHMS) Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 14, 2015. The information was verified by the guideline developer on September 18, 2015.

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